

1 **USE OF 4-ANDROSTENE-3,6,17-TRIONE TO ELEVATE TESTOSTERONE LEVELS AND**  
2 **THE TESTOSTERONE / ESTROGEN RATIO IN MALES**

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8 **FIELD OF THE INVENTION**

9 The present invention involves the use of 4-androstene-3,6,17-trione to stimulate endogenous  
10 testosterone production in males, while leaving estrogen levels relatively unaffected. It also involves  
11 the use of 4-androstene-3,6,17-trione to increase the testosterone/estrogen (T/E) ratio in males.

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14 **BACKGROUND OF THE INVENTION**

15 Testosterone is the hormone responsible for secondary sexual characteristics in males. Normal levels  
16 of testosterone are necessary for the full expression of the physical, psychological, and sexual  
17 characteristics of mature manhood. Estrogen is the hormone responsible for the secondary sexual  
18 characteristics in females. Males too produce estrogen, and its presence in precise amounts is  
19 necessary for the activity of testosterone to be fully generated.

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**SUMMARY OF THE INVENTION**

3        It is an object of the invention to provide a method of increasing testosterone levels while  
4    preventing increases in estrogen levels. Administration of 4-androstene-3,6,17-trione has been found  
5    to be effective and successful.

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1                   DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

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3           While absolute levels of testosterone and estrogen are of great importance to the male, the *ratio*  
4           of testosterone to estrogen (T/E ratio) should also be within a certain range for a male to exhibit  
5           maximal endocrinological health. Specifically, it is the presence of an abnormally low T/E ratio that  
6           is most problematic. If this ratio is too low then estrogen related disorders like gynecomastia and  
7           excessive bodyfat deposition can develop. Sex drive may suffer. Estrogen also increases the  
8           production of Sex Hormone Binding Globulin (SHBG), which then further decreases the biologically  
9           active free testosterone available in the system. Additionally, a low testosterone/estrogen ratio has  
10           been associated with the increase risk of developing benign prostate hypertrophy (BPH).

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12           It is important to note here however that estrogen is still an important hormone in men, and  
13           normal levels of estrogen are necessary for optimal bone density, cognitive function, cardiovascular  
14           health, and sexual function.

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16           As men increase in age, a gradual decrease in testosterone production is often seen. A decrease in  
17           testosterone production can be responsible for many age related disorders such as decreased strength  
18           and muscle mass, decreased cognitive function, and decreased libido.

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20           The decrease in testosterone production in older males often is not accompanied by a concomitant  
21           decrease in estrogen production. Consequently, an undesirable T/E ratio is then established. It is  
22           once again important to note that this decrease is not representative of an unhealthy increase in

1 estrogens, but rather due to a decrease in testosterone levels towards to the low normal or  
2 subphysiological range.

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4 The usual treatment for testosterone deficiency is the administration of exogenous androgens.  
5 These are given usually by injection (i.e. testosterone cypionate), transdermal administration (i.e.  
6 Andro-Gel®) or by the administration of synthetic orally active androgens (i.e. methyltestosterone).  
7 The orally active androgens however have significant liver toxicity so they have gone out of favor.  
8 Injections are less toxic but they are inconvenient and do not give steady blood levels of hormone.  
9 Transdermal androgens are the most convenient and pharmacokinetically favorable however even  
10 they are not without drawbacks. All exogenous androgens, including transdermals, lead to shutdown  
11 of the hypothalamic pituitary testicular axis (HPTA) and consequently induce testicular atrophy.  
12 Furthermore, exogenous androgens do not necessarily ameliorate the abnormally high T/E ratio seen  
13 in many older hypogonadal males. The exogenous androgens can still over-aromatize to estrogens  
14 and so even though androgen levels are back to normal, the T/E ratio may remain relatively  
15 unchanged.

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17 It is known that the HPTA is regulated by both estrogens and androgens in males. The more  
18 powerful regulator however is estrogen. In males, circulating testosterone is extensively metabolized  
19 into estradiol at the hypothalamus, and this estradiol then is available to immediately bind to  
20 hypothalamic estrogen receptors. The end results is a decrease in the secretion of gonadotropin  
21 releasing hormone (GnRH).

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1       GnRH is a hormone that is responsible for signaling the pituitary gland to release gonadotropins  
2       – specifically LH and FSH. These hormones then are released into the bloodstream where they travel  
3       to the testes and stimulate the production of testosterone and the synthesis of sperm.

4

5       It is also known that administration of anti-estrogen drugs to males causes a pronounced up-  
6       regulation of testosterone production by interfering with the normal estrogen mediated negative  
7       feedback system that starts at the hypothalamus.

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9       There are two kinds of anti-estrogen drugs. The first class is estrogen receptor antagonists  
10      (ERA's). Examples of these are tamoxifen and clomiphene. These drugs bind to the estrogen  
11      receptor but do not activate the estrogen responsive genes like normal estrogens do. They compete  
12      with the estrogen receptor and block out the endogenous active estrogens. These drugs however  
13      typically have a certain degree of pro-estrogenic activity and therefore can act like real estrogens at  
14      certain tissues. They therefore are not purely anti-estrogenic.

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16       Furthermore, ERA's lead to an increase in the levels of estrogens in the blood due to their  
17      stimulatory effect on the production of androgens – which are estrogen precursors. As a result, there  
18      can be a significant “estrogenic rebound” when the ERA's are discontinued.

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20       The other kind of anti-estrogens are aromatase inhibitors. Examples of these are testolactone and  
21      anastrazole. These compounds work by blocking and inactivating the aromatase enzyme. The  
22      aromatase enzyme is responsible for the formation of estrogens from androgenic precursors. In men,  
23      the two major precursors for estrogen biosynthesis are testosterone and androstenedione. Aromatase

1   inhibitors therefore prevent the actual formation of estrogen in the body, as opposed to receptor  
2   antagonists which merely block the activity of circulating estrogens. Since aromatase inhibitors do  
3   not lead to any sort of incidental pro-estrogenic activity like the receptor antagonists do, they are the  
4   cleaner anti-estrogens and therefore more preferred.

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6       Also, with aromatase inhibitors there is no estrogenic rebound upon discontinuation, since  
7   estrogen levels are not elevated. There simply is a gradual return to the baseline homeostatic sex  
8   hormone levels that were present before therapy was commenced.

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10      4-androstene-3,6,17-trione (a-trione) is a metabolite of androstenedione that has been shown to  
11   have aromatase inhibiting activity in-vitro. It has never been tested in humans however, and in the  
12   course of our research we decided to examine its effect on the male endocrinological profile.

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14      What we discovered was that a-trione produced a very marked increase of testosterone while  
15   exhibiting only a small, barely significant decrease in estradiol. This indicated that an improvement  
16   in the T/E ratio was achieved, while estrogen levels were still maintained within the healthy normal  
17   range. This makes the use of a-trione superior to most other aromatase inhibitors as a means of  
18   improving the T/E ratio. Specifically, because a-trione does not adversely effect estrogen production  
19   while other aromatase inhibitors tend to suppress estrogens down to the subphysiological range.

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21      Example

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1 Six male subjects, aged 32-40 years of age, were prescreened via a medical doctor for  
2 endocrinological abnormalities. The subjects' physical characteristics were: height 177.38 +/- 8057  
3 cm, weight 88.8 +/- 13.65 kg, body fat percentage 14.9 +/- 3.5%. Subjects ingested 300mg a-trione  
4 bid for three weeks as part of an open label design. Resting AM blood draws were taken at 0, 1, 2,  
5 and 3 weeks of supplementation. Table 1 indicates the changes in endocrine markers over the time  
6 evaluated. Results were analyzed using a Repeated Measures-ANOVA design with paired samples t-  
7 tests as appropriate. The results indicate that a-trione can increase testosterone levels (+88%)  
8 substantially while affecting estrogen only slightly (-11%). Therefore, a-trione can raise the T/E  
9 ratio while leaving estradiol in the safe physiological range.

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Endocrine Marker	Week 0	Week 1	Week 2	Week 3
Total Testosterone (ng/dL)	443.67 $\pm$ 59.07	701.17 $\pm$ 36.85	752.17 $\pm$ 78.11	835.33 $\pm$ 124.74
Free Testosterone (nmol/L)	126.67 $\pm$ 31.99	216.67 $\pm$ 33.64	252.33 $\pm$ 53.40	285.67 $\pm$ 69.22
Sex Hormone Binding Globulin (SHBG) (nmol/L)	21.83 $\pm$ 4.36	20.5 $\pm$ 3.83	19.5 $\pm$ 5.54	18.83 $\pm$ 6.18
Estradiol (pg/mL)	16.5 $\pm$ 1.38	16.5 $\pm$ 2.93	14.8 $\pm$ 2.93	14.67 $\pm$ 2.94
Dihydrotestosterone (ng/dL)	33.33 $\pm$ 3.56	39.83 $\pm$ 7.88	45.83 $\pm$ 14.72	47.5 $\pm$ 8.17
T/E Ratio	269/1	425/1	508/1	569/1

1       The average optimal daily dose of a-trione is 600mg a day. The effective dosage range however  
2       can extend from 100mg to 1000mg per day.

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4       A-trione can be administered orally, by injection, transdermally, intranasally, sublingually, or by  
5       any other commonly accepted pharmaceutical route. For convenience purposes however the  
6       preferred mode of administration is oral.

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8       Oral compositions may include tablets, capsules, dragees, liquid suspensions, or any other  
9       common oral formulation.

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